Single-Nucleotide Polymorphisms in *SMARCA2* as Related to Frontal Lobe Volume in Individuals with Schizophrenia.

Sarah M. Casey[1], Eric A. Epping[2], Thomas H. Wassink[2,3]

Department of Biochemistry[1], Department of Psychiatry[2], Interdisciplinary Program in Genetics[3]
University of Iowa Carver College of Medicine, Iowa City, IA

Abstract

Schizophrenia is a debilitating mental disorder that affects approximately 1% of the world population and is associated with delusions, disorganized speech and behavior, hallucinations, and abnormal brain structure and function. The risk of developing schizophrenia is associated with both environmental and genetic risk factors. Schizophrenia is genetically heritable; it has been found that offspring have a 10% chance of inheriting the disease from an affected parent. Because of this genetic heritability, searches for schizophrenia genes have been long underway using genome-wide association studies (GWAS). One GWAS discovered gene is *SMARCA2*, a member of the SWI/SNF chromatin-remodeling complex. Single-nucleotide polymorphisms (SNPs) in *SMARCA2* have also been associated with changes in gene expression. Koga, et al. associated SNPs in rs3763627 and rs3793490 with low *SMARCA2* expression levels in the postmortem prefrontal cortex. Allelic determination of these two SNPs was performed for a selection of individuals with Schizophrenia and healthy controls using TaqMan genotyping assays. The data set was combined with magnetic resonance imaging (MRI) scans and calculated brain lobe volumes for each individual sample. It was found that the genotype GG in rs3793490 in affected individuals showed decreased frontal lobe gray matter volumes when compared to affected individuals who are T-carriers in the same SNP. However, this result cannot be concluded as statistically significant due to the small sample size of the GG group.

TaqMan Assay Procedure

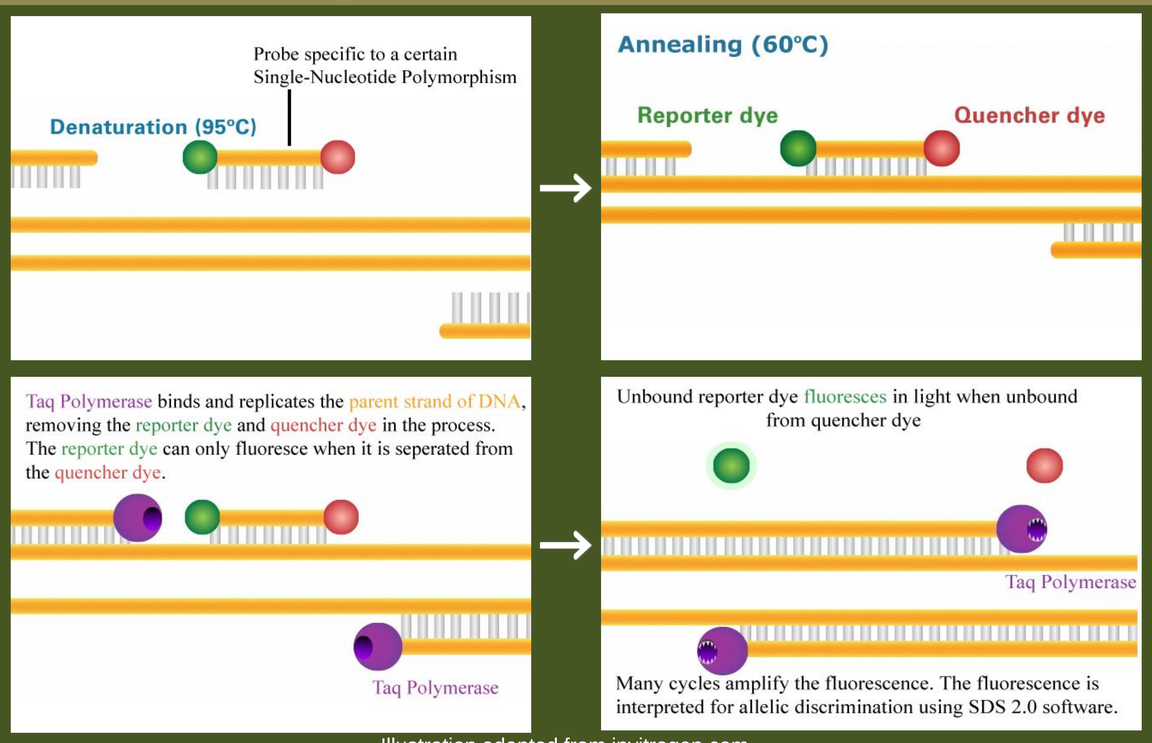


Illustration adapted from invitrogen.com

Genotype Frequencies

484 Samples
rs3763627 TaqMan Assay
↓
PRISM 7900HT/SDS 2.0

Probands	Controls
AA : 244	AA : 140
AT : 54	AT : 42
TT : 2	TT : 2
Experimental Frequency	**Experimental Frequency**
AA : 0.761	AA : 0.813
AT : 0.228	AT : 0.180
TT : 0.011	TT : 0.007

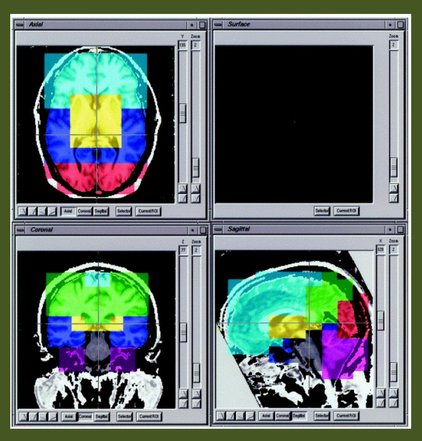
Allele Frequency X^2 = 1.91
DF = 1
***p*-value = 0.167**

566 Samples
rs3793490 TaqMan Assay
↓
PRISM 7900HT/SDS 2.0

Probands	Controls
GG : 6	GG : 4
GT : 87	GT : 49
TT : 278	TT : 142
Experimental Frequency	**Experimental Frequency**
GG : 0.016	GG : 0.021
GT : 0.235	GT : 0.251
TT : 0.749	TT : 0.728

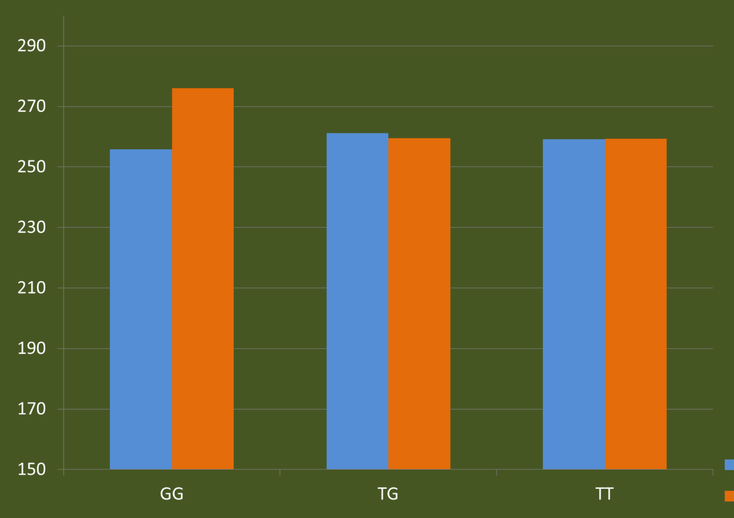
Allele Frequency X^2 = 0.349
DF = 1
***p*-value = 0.555**

Lobe Volume Determination



- Lobe volumes were determined using BRAINS software developed at the University of Iowa
- Brain structures are programmed into the software by location
- MRI cross sections are compiled by the program and are used to estimate the total volume of the brain structure

Frontal Lobe Gray Matter Volume in rs3793490 Patients and Controls

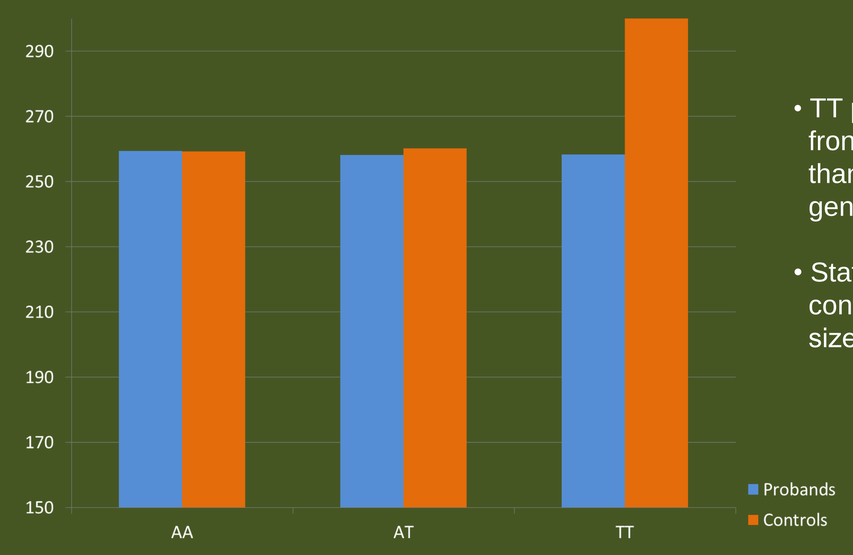


- Probands show a significantly lower frontal lobe gray matter volume than controls for the genotype GG
- GG probands show lower frontal lobe gray matter volume than probands or controls in the TG and TT genotypes
- Statistical relevance cannot be confirmed due to small sample size (GG frequency ≈ 0.017)

•Statistical analysis performed using JMP 8.0.2

*Measurements reported as the least squares mean in cubic centimeters

Frontal Lobe Gray Matter Volume in rs3763627 Patients and Controls



- TT probands show smaller frontal lobe gray matter volumes than controls of the same genotype
- Statistical relevance cannot be confirmed due to small sample size (TT frequency ≈ 0)

•Statistical analysis performed using JMP 8.0.2

*Measurements reported as the least squares mean in cubic centimeters

Conclusion

- The GG genotype in rs3793490 may be associated with decreased frontal lobe gray matter volumes in individuals with schizophrenia

References

• Koga, M., *et al*. (2009) Involvement of *SMARCA2*/BRM in the SWI/SNF chromatin-remodeling complex in schizophrenia. *Human Molecular Genetics, Vol.18, No.13*.
• American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th edition, text revised. Washington, DC: American Psychiatric Association, 2000.
• Loe-Mie, Y., *et al.* (2010) SMARCA2 and other genome-wide supported schizophrenia-associated genes: regulation by REST/NRSF, network organization and primate-specific evolution. *Human Molecular Genetics, Vol. 19, No.14*.